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4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2023-N-3167]

Notice of Opportunity for Public Comment on Proposal To Withdraw Approval of New Drug Application for PEPAXTO, Equivalent to 20 Milligrams Base per Vial

AGENCY: Center for Drug Evaluation and Research, Food and Drug Administration, HHS.

ACTION: Notice of opportunity for public comment.

SUMMARY: The Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA, the Agency) is proposing to withdraw approval of PEPAXTO (melphalan flufenamide) for injection, equivalent to (EQ) 20 milligrams (mg) BASE/VIAL, once every 28 days, new drug application (NDA) 214383, held by Oncopeptides AB (Oncopeptides). This notice is intended to provide an opportunity for public comment on CDER's proposed withdrawal of PEPAXTO, in accordance with the expedited withdrawal of approval procedures described in the Federal Food, Drug and Cosmetic Act (FD&C Act).

DATES: Either electronic or written comments on this proposal to withdraw PEPAXTO must be submitted by [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2023-N-3167 for "Notice of Opportunity for Public Comment on Proposal To Withdraw Approval of New Drug Application for PEPAXTO, Equivalent to 20 Milligrams Base per Vial." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at

https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Anuj Shah, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6224, Silver Spring, MD 20993-0002, 301-796-2246.

SUPPLEMENTARY INFORMATION:

I. Background

FDA approved NDA 214383 for PEPAXTO on February 26, 2021, under the accelerated approval pathway (section 506(c) of the FD&C Act (21 U.S.C. 356(c)) and 21 CFR part 314, subpart H) for use in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory drug, and one CD38-directed monoclonal antibody (triple class refractory).[1]

NDA 214383 relied on evidence from Trial OP-106 (ClinicalTrials.gov NCT number, NCT02963493), also known as HORIZON, a single-arm, open-label, phase 2 multicenter clinical trial that enrolled patients with relapsed or refractory multiple myeloma and who received at least two lines of prior therapy including an immunomodulatory drug and a proteasome inhibitor. The primary endpoint was overall response rate (ORR),[2] as assessed by the investigator.

At the time of approval under the accelerated approval pathway, the applicant was required to conduct an appropriate post-approval study to verify and describe the clinical benefit of PEPAXTO.[3] CDER has determined withdrawal of approval is warranted because the required post-approval confirmatory trial failed to verify clinical benefit and because available evidence demonstrates PEPAXTO is not shown to be safe or effective under its conditions of use. The Oncologic Drugs Advisory Committee (ODAC) convened on September 22, 2022, to discuss issues related to this proposed withdrawal. The ODAC voted 14 to 2 that the benefit-risk profile of melphalan flufenamide was not favorable for the currently indicated patient population. For

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[1] Most patients in the United States with relapsed disease will have been exposed to lenalidomide (an immunomodulatory agent), a proteasome inhibitor, corticosteroids, and an anti-CD38 monoclonal antibody after one or two lines of treatment, and retreatment with previously used agents or agents in the same class of drug can be effective.

[2] ORR was defined as the proportion of patients with a best confirmed response of stringent complete response, complete response, very good partial response, or partial response according to the International Myeloma Working Group Uniform Response Criteria.

[3] Section 506(c)(2)(A)(i) of the FD&C Act (as renumbered by the Consolidated Appropriations Act of 2023 (Pub. L. 117-328); see also 21 CFR 314.510.

additional background, please refer to CDER's letter to Oncopeptides Re: Section 506(c)(3)(B) Notice of Proposed Withdrawal of Approval; PEPAXTO (melphalan flufenamide) for injection; NDA 214383 ("Notice to Oncopeptides of Proposed Withdrawal of PEPAXTO") and CDER's Proposed Withdrawal of PEPAXTO Decisional Memorandum, available at Docket No. FDA-2023-N-3167, https://www.regulations.gov.

II. Legal Standard for Withdrawal of Approval

Section 506(c) of the FD&C Act, as amended most recently by the Consolidated Appropriations Act of 2023 (Pub. L. 117-328), describes the accelerated approval of new drug applications and the procedures and authority governing expedited withdrawal of approval. FDA has the legal authority to use the expedited procedures to withdraw approval of a product that has received accelerated approval if, among other reasons, "a study required to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit of the product fails to verify and describe such effect or benefit" (section 506(c)(3)(A)(ii) of the FD&C Act) or "other evidence demonstrates that the product is not shown to be safe or effective under the conditions of use." (section 506(c)(3)(A)(iii) of the FD&C Act.)

III. Explanation for the Proposed Withdrawal

CDER proposes to withdraw approval of PEPAXTO because the required confirmatory study, Trial OP-103, also known as OCEAN, failed to verify clinical benefit and because available evidence demonstrates PEPAXTO is not shown to be safe or effective under its conditions of use. More specifically, the results failed to show that PEPAXTO had a significant effect on the primary endpoint of progression-free survival. Furthermore, the observed median overall survival was 5.3 months shorter in the PEPAXTO arm compared to the control arm. After considering all the available data and the discussion at the ODAC held in September 2022, CDER recommends withdrawing the accelerated approval for PEPAXTO. Please refer to CDER's "Notice to Oncopeptides of Proposed Withdrawal of PEPAXTO" and "Proposed Withdrawal of PEPAXTO Decisional Memorandum" for additional explanation.

IV. Opportunity for Public Comment on CDER's Proposal To Withdraw Approval of PEPAXTO

In accordance with the expedited withdrawal of approval procedures described in section 506(c)(3)(B)(ii) and (iii) of the FD&C Act, CDER is providing an opportunity for public comment on its proposal to withdraw approval of NDA 214383 (PEPAXTO) through the issuance of a *Federal Register Notice*. FDA will consider any such public comments it receives in making its decision on CDER's proposal to withdraw approval of NDA 214383 (PEPAXTO) and make available on its website and in the public docket a summary of such comments and FDA's response to them.

Dated: August 21, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

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